Unusual reactivity of *N*-acyl imides: *N*-aroyl-1,2,4-dithiazolidine-3,5-diones as acyl isocyanate equivalents†

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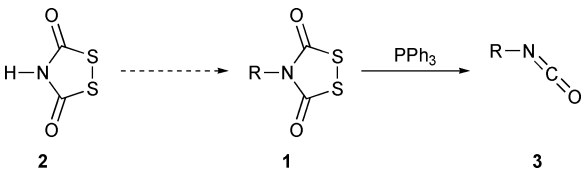
Received 22nd August 2008, Accepted 18th September 2008
First published as an Advance Article on the web 1st October 2008
DOI: 10.1039/b814677b

Crystalline samples of three *N*-aroyl-1,2,4-dithiazolidine-3,5-diones have been prepared as the first examples of a novel class of compound that displays the reactivity of an acyl isocyanate when treated with nucleophiles.

Recent studies in our laboratory have shown that *N*-alkyl-1,2,4-dithiazolidine-3,5-diones **1** can be prepared, using straightforward procedures,[1,2] from the parent heterocycle **2**.[3,4] Most significantly, they can be regarded as protected isocyanates **3**, the latter functionality being revealed on treatment with triphenylphosphine, under anhydrous conditions (Scheme 1).



Scheme 1 *N*-Alkyl-1,2,4-dithiazolidine-3,5-diones as isocyanate equivalents.

Acyl isocyanates **4** (Fig. 1) are very useful reagents, not only for the preparation of *N*-acyl ureas and *N*-acyl carbamates but also for the construction of a wide range of heterocycles by virtue of their ability to readily undergo addition to unsaturated compounds.[5–7] Such reagents are, however, considerably more reactive than their *N*-alkyl counterparts **3**, which can present substantial problems with their handling and long-term storage. A relatively small number of generally applicable methods are available for their preparation, most notably the reaction of acid chlorides with silver[8] or sodium[9] cyanate and the treatment of primary amides with oxalyl chloride.[10]

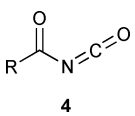


Fig. 1 *N*-Acyl isocyanates.

In view of our previous work, we initiated studies into the preparation of hitherto unknown‡ *N*-aroyl-1,2,4-dithiazolidine-3,5-diones **5** as possible acyl isocyanate **4** equivalents (Fig. 2).

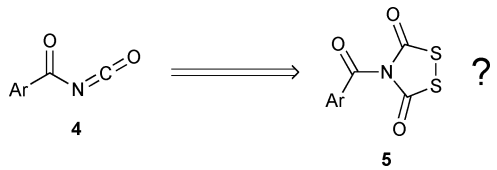
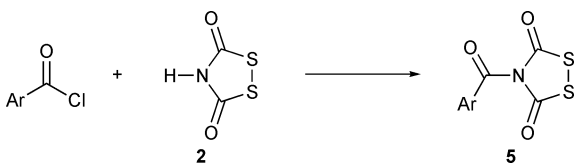


Fig. 2 *N*-Aroyl-1,2,4-dithiazolidine-3,5-diones as possible acyl isocyanate equivalents.

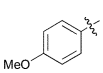
The logical approach to the preparation of *N*-acyl imides involves the treatment of the appropriate *N*-H imide with an acid chloride, under basic conditions. Indeed, Titherley and Hicks reported the preparation of *N*-benzoyl phthalimide in 1906 by the reaction between phthalimide and benzoyl chloride in pyridine, from which the desired product was precipitated by the addition of ethanol.[11] Attempts to modify this methodology for the use of 1,2,4-dithiazolidine-3,5-dione **2** failed to give the desired product with benzoyl chloride and similar approaches using other bases such as Hünig's base, caesium carbonate and potassium *tert*-butoxide also failed. It was found, however, that the desired reaction could be effected in dichloromethane using poly(4-vinylpyridine) as an insoluble base to simplify purification. Using this methodology, three novel *N*-aroyl-1,2,4-dithiazolidine-3,5-diones **5** were prepared (Scheme 2 and Table 1).†



Scheme 2 *N*-Aroylation of 1,2,4-dithiazolidine-3,5-dione. *Reagents and conditions:* poly (4-vinylpyridine) (1 equiv.), CH_2Cl_2, 0 °C to reflux, 24 h.

The crude products obtained were found (by ^1H and ^{13}C NMR) to be very impure and they generally contained significant quantities of the primary amides corresponding to the acid

Table 1 Preparation of *N*-aroyl-1,2,4-dithiazolidine-3,5-diones

Entry	Ar	Product	Yield (%)
1		**5a**	22
2		**5b**	18
3		**5c**	14

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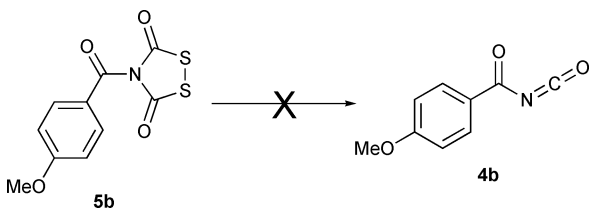
† Electronic supplementary information (ESI) available: General experimental procedure for the preparation of **5a–5c** and analytical/spectroscopic data for these compounds. See DOI: 10.1039/b814677b

chlorides used. The fact that the quantity of the amide increased on attempting to remove by-products using aqueous sodium bicarbonate solution suggested that they were the result of hydrolytic cleavage of the heterocycle in the products **5**. Despite attempts to exclude all water from the reaction mixtures by its azeotropic removal from the poly(4-vinylpyridine) with benzene prior to use, we could not significantly reduce the quantity of amide by-product formed and attempts to purify the crude reaction products by chromatography on silica gel unsurprisingly led to apparent complete decomposition of the required products **5**. Fortunately, however, the *N*-aroyl-1,2,4-dithiazolidine-3,5-diones **5** proved to be highly crystalline and whilst they could only be obtained in relatively low yields, they could be crystallised in an analytically pure form from chloroform, by slow diffusion of pentane, layered carefully above the solution. Interestingly, it was clear that the crude products resulting from the reactions carried out at reflux contained significantly fewer by-products than those from reactions carried out at lower temperatures. The resulting crystalline solids have subsequently been stored in air for several months with no noticeable decomposition.

Preparation of 4-methoxybenzoyl isocyanate **4b** from *N*-(4-methoxybenzoyl)-1,2,4-dithiazolidine-3,5-dione **5b** by desulfurisation with solid-supported triphenylphosphine was attempted at 40, 80 and 110 °C in dichloromethane, benzene and toluene respectively (Scheme 3). Shorter reaction times appeared to result in no reaction, **5b** still being present, and extended reaction periods (up to 48 h) gave 4-methoxybenzamide **6** (Fig. 3) as the only isolable product after filtering off the solid-supported reagent and evaporation of the solvent, despite care being taken to exclude moisture at all times.



Scheme 3 Attempted is isocyanate generation from *N*-(4-methoxybenzoyl)-1,2,4-dithiazolidine-3,5-dione. *Reagents and conditions:* solid-supported triphenylphosphine (1.3 equiv.), solvent (CH_2Cl_2, C_6H_6 or PhMe), reflux, 24–48 h.

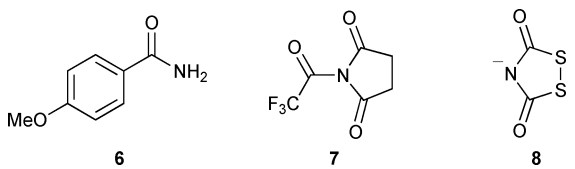
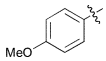
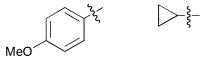
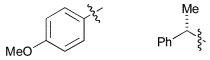
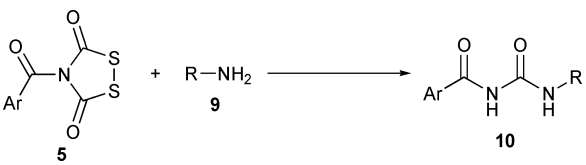


Fig. 3 4-Methoxybenzamide, *N*-(trifluoroacetyl)succinimide and the conjugate base of 1,2,4-dithiazolidine-3,5-dione.

Given the ability of *N*-(trifluoroacetyl)succinimide **7** (Fig. 3) to act as an "active ester-type" reagent for trifluoroacetylation,[12] the reactivity of *N*-aroyl-1,2,4-dithiazolidine-3,5-diones **5a–c** towards amines and alcohols was investigated. In view of the low pK_a value of **2** ($pK_a = 2.85$, $I = 0.163$, 25.6 °C)[13] compared with that of succinimide ($pK_a = 9.59$, $I = 0.5$, 25 °C),[14] it was initially anticipated that the conjugate base of 1,2,4-dithiazolidine-3,5-dione **8** (Fig. 3) would be a very good leaving group in this system, giving similar reactivity. When treated with a range of primary amines **9** (in THF or toluene under reflux), however, **5a–c** gave the corresponding *N*-aroyl ureas **10** in reasonable yields, apparently produced by nucleophilic attack at a carbonyl group of the heterocyclic ring rather than the exocyclic carbonyl group as originally expected (Scheme 4). The results for these experiments are summarised in Table 2 and they suggest that *N*-aroyl-1,2,4-dithiazolidine-3,5-diones **5** are capable of reacting as acyl isocyanate **4** equivalents.

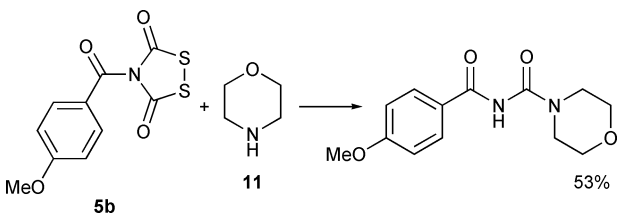
Table 2 *N*-Aroyl urea formation from *N*-aroyl-1,2,4-dithiazolidine-3,5-diones and primary amines

Entry	Ar	R	Solvent	Product	Yield (%)
1		^{t}Bu	THF	**10a**	86
2		^{t}Bu	THF	**10b**	64
3			THF	**10c**	57
4			PhMe	**10d**	71
5		^{t}Bu	THF	**10e**	64



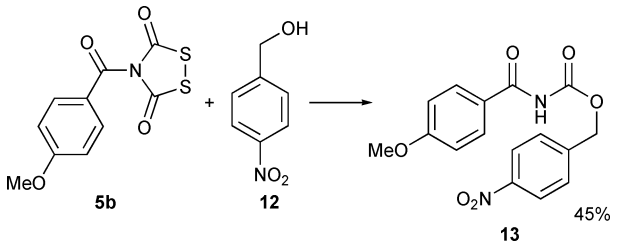
Scheme 4 *N*-Aroylurea formation from *N*-aroyl-1,2,4-dithiazolidine-3,5-diones and primary amines. *Reagents and conditions:* amine (1 equiv.), THF or PhMe, reflux, 24 h.

A secondary amine (morpholine, **11**) gave a similar result on reaction with *N*-(4-methoxybenzoyl)-1,2,4-dithiazolidine-3,5-dione **5b** (Scheme 5) and 4-nitrobenzyl alcohol **12** also produced the corresponding *N*-(4-methoxybenzoyl)urethane **13** under essentially identical conditions (Scheme 6).

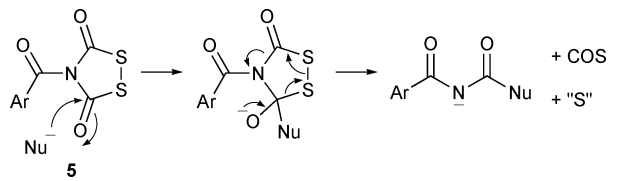


Scheme 5 *N*-Aroylurea formation from *N*-(4-methoxybenzoyl)-1,2,4-dithiazolidine-3,5-dione and morpholine. *Conditions:* THF, reflux, 18 h.

Alkaline hydrolysis of *N*-alkyl-1,2,4-dithiazolidine-3,5-diones **1** is believed to occur *via* nucleophilic attack of hydroxide at a carbonyl group of the heterocycle[15] and nitrogen nucleophiles are also known to form ureas directly with these compounds,[1,16] suggesting the mechanism shown in Scheme 7 is appropriate



Scheme 6 *N*-Aroylcarbamate formation from *N*-(4-methoxybenzoyl)-1,2,4-dithiazolidine-3,5-dione and 4-nitrobenzyl alcohol. *Conditions:* THF, reflux, 24 h.



Scheme 7 Proposed mechanism for nucleophilic ring-opening of *N*-aroyl-1,2,4-dithiazolidine-3,5-diones.

for *N*-aroyl-1,2,4-dithiazolidine-3,5-diones **5** behaving as acyl isocyanates **4**.

In summary, we have demonstrated the first method for the preparation of *N*-aroyl-1,2,4-dithiazolidine-3,5-diones **5**, a novel class of compound that shows the reactivity of an acyl isocyanate **4** in reactions with amine and alcohol nucleophiles. Whilst there is clearly room for improvement in the method for the preparation and isolation of these compounds, they represent a potentially very useful, crystalline and air stable alternative to a difficult to handle, yet important, class of reagent.

Acknowledgements

We thank AstraZeneca and EPSRC for funding to V. M. A., the EPSRC National Mass Spectrometry Service Centre (Swansea, UK) for mass spectra and Dr Stephen J. Simpson (Exeter, UK) for NMR work.

Notes and references

‡ We previously reported (tentatively) the possible preparation of *N*-benzoyl 1,2,4-dithiazolidine-3,5-dione,[1] however, the studies described herein revealed that our original structural assignment was incorrect.

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